**Computational and Experimental Cocrystal Screening of Tiopronin and Dapagliflozin APIs**

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**Purpose:**

Development and validation of novel hybrid virtual coformer screening model, which integrates COSMO-RS with machine learning to account for both miscibility in the amorphous phase and crystallinity contributions to cocrystallization.

**Methods:**

We developed a novel COSMO-RS + Δ-ML approach using a dataset of 178 cocrystal observations. The model was validated against published experimental cocrystal screening data for nine APIs and then applied to guide targeted experimental screenings for tiopronin and dapagliflozin. Experimental work involved 100 reactive crystallization studies per API (5 solvents × 20 virtually selected coformers), followed by slow evaporation crystallization when necessary.

**Results:**

Retrospective validation against reported studies demonstrated superior performance of the new virtual screening approach compared with the pure COSMO-RS method. The in-house experiments led to the discovery and characterization of the first anhydrous 4,4′-bipyridine cocrystal of tiopronin, as well as two anhydrous cocrystals of dapagliflozin: citrate and a novel bis-L-proline cocrystal.

**Conclusions:**

The integrated workflow—combining COSMO-RS + Δ-ML virtual screening with targeted experimental validation—provides a powerful strategy to accelerate and de-risk pharmaceutical coformer screening projects.

**Keywords:**

Cocrystal, virtual coformer screening, crystallization